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Mini Review Open Access

Prenatal Exposures to Environmental Agents or Drugs Promote the Development of Diseases Later in Life

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Abstract

Prenatal or early postnatal exposure to several agents displaying hormonal action causes persistent quantitative and qualitative changes in hormone receptors in various cell-types. Exposure must occur during the windows of susceptibility, which occurs at specific times for each cell-type and hormone receptor. These alterations, that persist through life, are induced by the mechanism of epigenetic imprinting (cell programming). Studies performed in our Labs and elsewhere found that not only hormones or agents displaying hormone action, but also those not displaying this activity, may induce the mechanism of imprinting; among them, lead and arsenic.

Keywords: Prenatal exposures; Lead; Arsenic; Dioxins; Epigenomic imprinting

Background and Methodology

The present mini-review describes the delayed effects of prenatal exposure to the most conspicuous environmental agents reported to increase several diseases risk later in life. The chosen agents are examples of a wide mechanism involving numerous agents, to which physicians and other health professionals should pay attention. Examples of less known food pollutants or drugs are also presented.

Selected agents were chosen based on the best known mechanistic and toxicological characteristics and also on most clinically relevant adverse effects on human health. Less relevant effects were excluded.

Searches were performed through Pubmed/Medline, ISI, and other sources, without date restrictions. References were selected considering the finding first report, and the most detailed description.

Overview of Prenatal Exposure and the Mechanisms of Epigenomic Imprinting

Prenatal or early postnatal exposure to several agents displaying hormonal action causes persistent quantitative and qualitative changes in hormone receptors in various cell-types [1]. Exposure must occur during the windows of susceptibility, which occurs at specific times for each cell-type and hormone receptor. These alterations, that persist through life, are induced by the mechanism of epigenetic imprinting (cell programming) [2,3]. Studies performed in our Labs [2-5] and elsewhere found that not only hormones or agents displaying hormone action, but also those not displaying this activity, may induce the mechanism of imprinting; among them, lead and arsenic. Imprinting-inducing agents may be found among environmental pollutants, pharmaceuticals, drugs of abuse, food additives and anthropogenic or natural compounds present in food [4-6]. It was proposed that changes induced by the mechanism of imprinting are the root for the development of various diseases and neurobehavioral changes later in life [5,6]. For humans, the first evidence that prenatal exposure to a pharmaceutical agent (the synthetic estrogen diethylstilbestrol) induces imprinting emerged from clear cell cervicovaginal adenocarcinoma development in young women whose mothers received treatment with diethylstilbestrol during pregnancy [7]. Prenatal exposure to the same agent induced the development of similar tumors in experimental animals [8], induced an increase in uterine estrogen receptors [1] and caused a great potentiation of a response to estrogen in a uterine cell-type [9] at older ages.

Knowledge of the etiology of the different diseases aims to the development of protective measures to decrease their incidence and to find new therapeutic approaches. Genomic characterization is important to analyze the risk for various pathologies, such as cancer, autoimmune diseases, neurodegenerative pathologies. However, somatic cells genome may be permanently altered by epigenetic changes through methylation and demetylation processes thus modifying the susceptibility to develop these diseases. For instance, methylation changes were reported in brain of patients affected with various Parkinson [10], Alzheimer [11] and Huntington [12] diseases and probably multiple sclerosis [13,14]. Several conditions during gestation may modulate brain development, such as maternal diet, stress and diseases (diabetes, hypertension), or maternal treatment with pharmaceuticals. The above epigenetic factors may affect brain cell programming and they may condition susceptibility or resistance for the development of various neurodegenerative diseases [15].

The best known imprinters from the environmental pollutants are lead, arsenic, cadmium, benzopyrene and various dioxins, furans, polychlorinated biphenyls and pesticides (DDT, DDE, methoxychlor, chlordecone, parathion, malathion, paraquat, cypermethrin and cyhalothrin). Among drugs, diethylstilbestrol, anti-epileptic drugs, and neuroleptic agents binding barbiturate or benzodiazepine receptors. Drugs of abuse such as cocaine, opiates, ketamine, toluene, tetrahydrocannabinol, ethanol and tobacco smoking. Food additives: nitrites, caffeine, aspartame, etc. Other agents found in food include bisphenol-A, nonylphenol, phthalates, acrylamide and steroids used as farm animal growth promoters. High prenatal lipid feeding induces

cholesterol homeostatic memory [16] and alters blood estrogen levels during adulthood, which is a risk factor for breast cancer [17]. Therefore dietary factors in early life determine the prevalence of various diseases in adulthood.

Below we describe examples of some of the delayed adverse effects of early exposure to the most known imprinters: lead, arsenic, dioxins, antiepileptic drugs and bisphenol-A.

Prenatal exposure to lead

In prepubertal rats, prenatal exposure to lead potentiates two non-genomic responses to estrogen, while in the absence of prenatal exposure, lead inhibits these responses [4]. This finding led us to propose that epigenetic imprinting is a mechanism that developed some time in the evolution and allowed species survival under unfavorable environmental conditions since it provided protection neutralizing adverse effects of chronic exposure to lead and perhaps other agents [4,5].

In addition to early developmental lead exposure which contributes to fertility inhibition in humans and experimental animals [18], the most relevant effects of early lead exposure are those affecting central nervous system. Several neurological and neurobehavioral changes attributed to lead exposure were reported in countries with high lead pollution levels [19-21]. It causes learning impairment, lower IQ scores, increased school failure [22,23]. A deficit in the IQ scores was detected in children with lead blood levels of 9 μg/dL [21]; IQ declined by 7.4 points as lifetime average blood lead concentrations increased from 1 to 10 μg/dL [24]. Blood lead levels from 5 to 9 μg/dL increased in the percentage of students requiring special education [25]. Perinatal or infant human lead exposure causes the development of a hyperactive and aggressive behavior [19]; lead content in tibia at the age of 12 years, was associated to increased risk for antisocial and delinquent behavior [26]. Data on year lead amounts used in different countries revealed an association with crime indexes. Despite divergent international crime trends, regression R^2 is near its peak in each nation (in USA, Australia, France, Italy, West Germany, Britain, New Zealand, Canada and Finland) with a lag of 19 years [27]. Following prenatal exposure to lead, a permanent increase in the affinity of δ-opioid receptors [28] was reported in the rat brain. This finding lead us to hypothesize that early exposure to lead may facilitate addiction to drugs of abuse (opiates and stimulants) in countries with high lead pollution [2]. This hypothesis was confirmed in experimental animals by studies of other authors [29-33].

Prenatal exposure to arsenic

Arsenic prenatal exposure affects respiratory functions later in life. Drinking water in the Chilean city of Antofagasta had very high arsenic levels between 1958 and 1970 (around 0.8 mg/L). Antofagasta mortality rates in the period 1989-2000 were compared with the rest of Chile, focusing on subjects born during or just before the peak exposure period and who were 30-49 years old at the time of death (prenatally exposed). They were compared to the cohort born before the high-exposure period (1950-1957) and exposed in childhood later but not prenatally. Standard mortality ratio for bronchiectasis in prenatally exposed population was four times higher than in non prenatally exposed [34].

Prenatal exposure to polychlorinated biphenyl/dioxins

Polychlorinated biphenyl/dioxin prenatal exposure imprints changes in the immune system, central nervous system and mainly male reproductive system in humans. It is associated with total number of T cells and the number of CD8+ (cytotoxic), TcRαβ+, and TcRγδ+ T cells increase in infants [35], and immune depression that persists through childhood, in prenatally exposed children [36]. A decrease in lung function was also associated with perinatal exposure to background levels of dioxins [37]. Prenatal exposure to polychlorinated biphenyls and dibenzofuranes determine, at young adult age, persistent alterations in sperm quality and inhibits spermatozoid capacity to penetrate hamster oocytes; therefore, it may cause male infertility [38]. Prenatal exposure to dioxins, furans or polychlorinated biphenyls was reported to determine feminization of 7-8 year old male children gender-related play behavior [39]. In experimental animals, it was shown that prenatal exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin also determines demasculinization and feminization of sex behavior in male rats [40,41], which was not associated with alterations in estrogen receptor binding or sexually differentiated brain nuclei volumes [41]. Permanent morphologic and behavior male demasculinization, feminization, and decrease in fertility were also reported in rats and hamsters following prenatal exposure to dioxin [42].

Examples of prenatal exposure to drugs or food pollutants

Prenatal exposure to some antiepileptic drugs increases the risk of behavioral problems in preschool children [43]. Bisphenol-A prenatal or neonatal exposure of experimental animals was associated to advancement of puberty and affected sexual dimorphic hypothalamic areas by increasing oxytocin immunoreactive neurons [44], development of several ovary and uterine pathologies [45] and early adipogenesis [46].

Concluding Remarks

The chosen selected examples of pollutants and drugs to which human population is exposed should alert countries governments to endorse stricter standards and tighten legislation to protect future generations from diseases that may develop following prenatal or early infant exposures. While imprinting may be a positive mechanism to preserve species through evolution, prenatal exposure to pollutants or drugs in human population clearly increase the risk for several diseases. We also alert scientific communities on probable effects of many additional agents that had not been yet investigated for its potential epigenetic imprinting.

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